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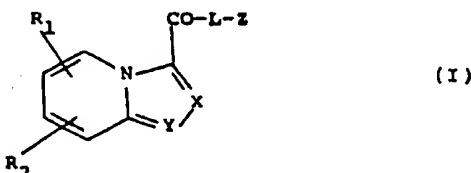
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㉒ Azabicyclic compounds, process for their preparation, and their pharmaceutical use.

㉓ Compounds of formula (I), or a pharmaceutically acceptable salt thereof:



wherein

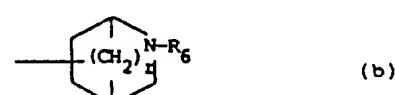
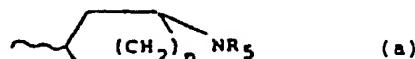
L is NH or O;

X is N or CR₃ wherein R₃ is hydrogen or C₁₋₆ alkoxy;

Y is N or CR₄ wherein R₄ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphinyl, C₁₋₆ acyl, cyano, C₁₋₆ alkoxy carbonyl, C₁₋₆ acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkyl C₁₋₆ alkyl or disubstituted by C₄ or C₆ polymethylene; phenyl or phenyl C₁₋₆ alkyl group optionally substituted in the phenyl ring by one or two of halogen, C₁₋₆ alkoxy or C₁₋₆ alkyl groups.

R₁ and R₂ are independently selected from hydrogen, or halogen;

Z is a group of formula (a), (b) or (c):



wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R₆ or R₈ is C₁₋₄ alkyl; having 5-HT₁ antagonist activity, a process for their preparation and their use as pharmaceuticals.

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TITLE UNIFIED

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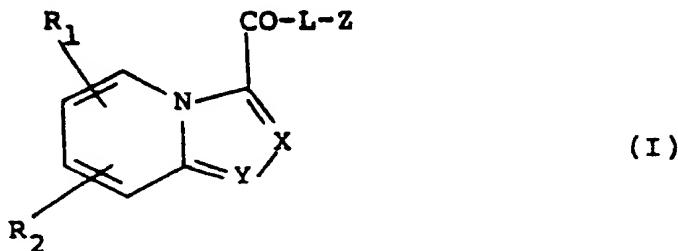
NOVEL COMPOUNDS

This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

GB 2100259A and 2125398A, and EP-A-158265 describe esters and amides having an azabicyclic side chain and possessing 5-HT₃ antagonist activity.

A class of novel, structurally distinct compounds has now been discovered. These compounds have 5-HT₃ antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



wherein

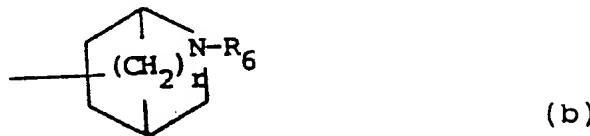
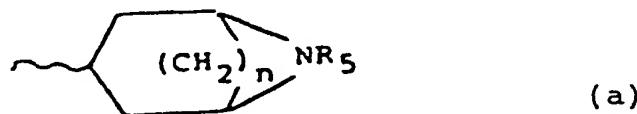
L is NH or O;

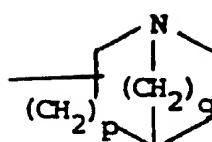
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- 2 -

X is N or CR₃ wherein R₃ is hydrogen or C₁₋₆ alkoxy;
Y is N or CR₄ wherein R₄ is hydrogen, halogen, CF₃,
C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆
alkylsulphonyl, C₁₋₆ alkylsulphanyl, C₁₋₇ acyl, cyano,
C₁₋₆ alkoxycarbonyl, C₁₋₇ acylamino, hydroxy, nitro or
amino, aminocarbonyl, or aminosulphonyl, optionally
N-substituted by one or two groups selected from C₁₋₆
alkyl, C₃₋₈ cycloalkyl, and C₃₋₈ cycloalkyl C₁₋₄ alkyl
or disubstituted by C₄ or C₅ polymethylene; phenyl or
phenyl C₁₋₄ alkyl group optionally substituted in the
phenyl ring by one or two of halogen, C₁₋₆ alkoxy or
C₁₋₆ alkyl groups.

14 R₁ and R₂ are independently selected from hydrogen, or
15 halogen;
16





(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R₅ or R₆ is C₁₋₄ alkyl.

Often L is NH.

Suitable values for X include N, or CR₃¹ wherein R₃¹ is hydrogen, methoxy, ethoxy, n- or iso-propoxy. Often X is N, CH or COMe.

Suitable values for Y include N, or CR₄¹ wherein R₄¹ is hydrogen, fluoro, chloro, bromo, CF₃, methyl, ethyl, methoxy, ethoxy, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, methylsulphinyll, ethylsulphinyll, acetyl, propionyl, cyano, methoxycarbonyl, ethoxycarbonyl, acetylarnino, hydroxy, nitro; and amino, aminocarbonyl, or aminosulphonyl, any of which may be optionally substituted by one or two methyl groups or by a cyclopentyl or cyclohexyl group or R₄¹ is phenyl or benzyl optionally substituted by one or two methyl, methoxy, bromo, chloro or fluoro groups. Often Y is N, CH or CCH₃, preferably CCH₃.

Values for R₁ and/or R₂ include hydrogen, fluoro, chloro or bromo. Preferably R₁ and R₂ are both hydrogen.

01 - 4 -
02 Preferably n is 2 or 3 and p, q and r are 1 or 2.

04 Examples of R₅/R₆ include as groups of interest C₁₋₃
05 alkyl such as methyl, ethyl and n- and iso-propyl.
06 R₅/R₆ is preferably methyl or ethyl, most preferably
07 methyl.

09 There is a group of compounds within formula (I)
10 wherein R₄ is hydrogen or C₁₋₆ alkyl and the remaining
11 variables are as defined in formula (I).

13 The pharmaceutically acceptable salts of the compounds
14 of the formula (I) include acid addition salts with
15 conventional acids such as hydrochloric, hydrobromic,
16 boric, phosphoric, sulphuric acids and pharmaceutically
17 acceptable organic acids such as acetic, tartaric,
18 maleic, citric, succinic, benzoic, ascorbic,
19 methanesulphonic, α -keto glutaric, α -glycerophosphoric,
20 and glucose-1-phosphoric acids.

22 The pharmaceutically acceptable salts of the compounds
23 of the formula (I) are usually acid addition salts with
24 acids such as hydrochloric, hydrobromic, phosphoric,
25 sulphuric, citric, tartaric, lactic and acetic acid.

27 Preferably the acid addition salt is the hydrochloride
28 salt.

30 Examples of pharmaceutically acceptable salts include
31 quaternary derivatives of the compounds of formula (I)
32 such as the compounds quaternised by compounds
33 R_a -T wherein R_a is C₁₋₆ alkyl, phenyl-C₁₋₆ alkyl or
34 C₅₋₇ cycloalkyl, and T is a radical corresponding to an
35 anion of an acid. Suitable examples of R_a include
36 methyl, ethyl and n- and iso-propyl; and benzyl and
37 phenethyl. Suitable examples of T include halide such

- 5 -

as chloride, bromide and iodide.

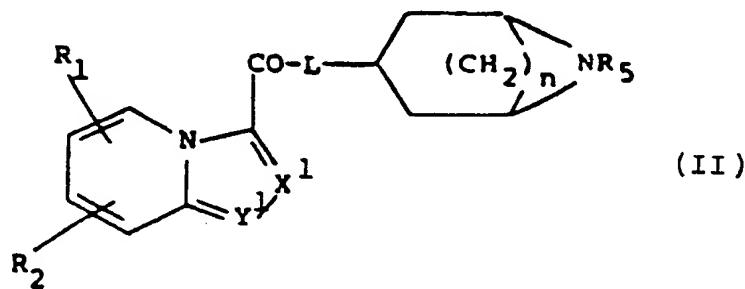
Examples of pharmaceutically acceptable salts also include internal salts such as N-Oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

It will also be realised that compounds of formula (I) may adopt an endo or exo configuration with respect to L. The endo configuration is preferred.

A group of compounds within formula (I) is of formula (II):

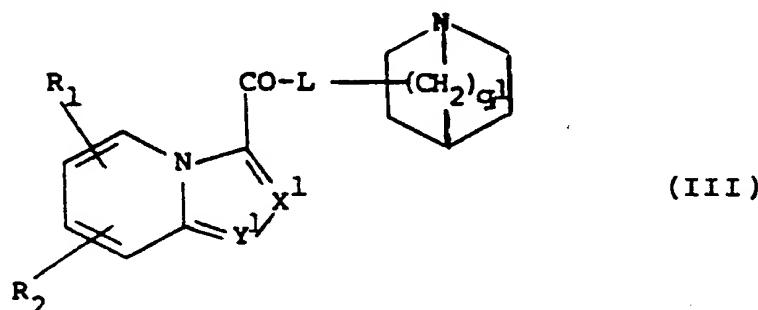


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01 wherein x^1 is N, H or COCH_3 , y^1 is N, H or $\text{C}-\text{R}_4^1$ as
 02 defined and the remaining variables are as defined in
 03 formula (I).

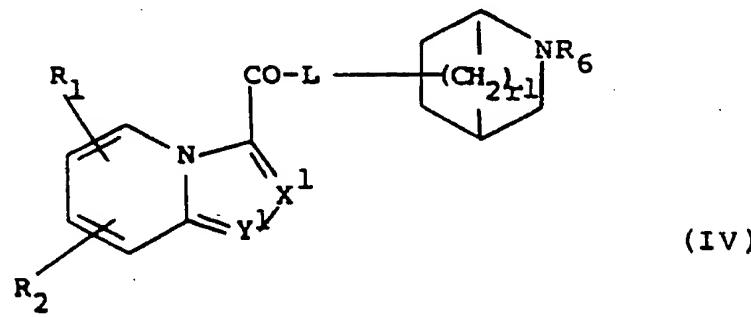
04
 05 Examples of the variables and preferred variables are
 06 as so described for corresponding variables in relation
 07 to formula (I).

08
 09 A further group of compounds within formula (I) is of
 10 formula (III):



24
 25 Examples of the variables and preferred variables are
 26 as so described for the corresponding variables in
 27 formula (I).

28
 29 There is a further group of compounds within formula
 30 of formula (IV):

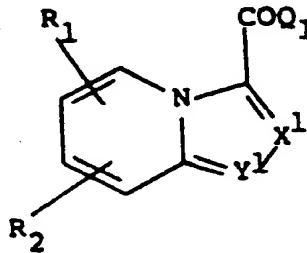


- 7 -

wherein r^1 is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

Examples of the variables and preferred variables are so described as the corresponding variables in formula (I).

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (V):



(V)

with a compound of formula (VI):



(VI)

or a reactive derivative thereof, when L is ():

wherein Q₁ is a leaving group; Z¹ is Z as defined or wherein R₅/R₆ is replaced by a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting any R₁ and/or R₂ group to another R₁/R₂ group respectively, converting Z¹, when other than Z,

01 - 8 -

02 to Z; and optionally forming a pharmaceutically
03 acceptable salt of the resultant compound of formula
04 (I).

05 Examples of leaving groups Q₁, displaceable by a
06 nucleophile, include halogen such as chloro and bromo,
07 C₁₋₄ alkoxy, such as CH₃O and C₂H₅O-, PhO-, or
08 activated hydrocarbyloxy, such as Cl₅C₆O- or Cl₃CO-

10 If a group Q₁ is a halide, then the reaction is
11 preferably carried out at non-extreme temperatures in
12 an inert non-hydroxylic solvent, such as benzene,
13 dichloromethane, toluene, diethyl ether,
14 tetrahydrofuran (THF) or dimethylformamide (DMF).
15 It is also preferably carried out in the presence of an
16 acid acceptor, such as an organic base, in particular a
17 tertiary amine, such as triethylamine, trimethylamine,
18 pyridine or picoline, some of which can also function
19 as the solvent. Alternatively, the acid acceptor can
20 be inorganic, such as calcium carbonate, sodium
21 carbonate or potassium carbonate. Temperatures of
22 0°-100°C, in particular 10-80°C are suitable.

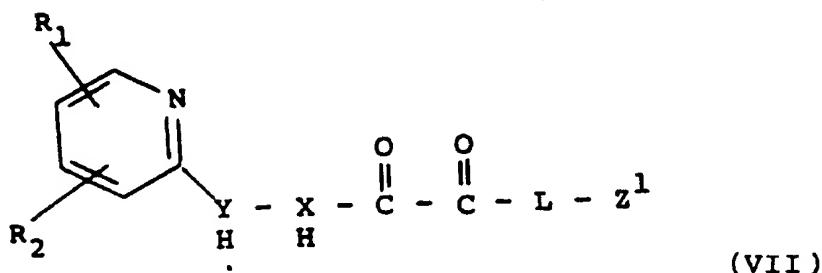
24 If a group Q₁ is C₁₋₄ alkoxy, phenoxy or activated
25 hydrocarbyloxy then the reaction is preferably carried
26 out in an inert polar solvent, such as toluene or
27 dimethylformamide. It is also preferred that the group
28 Q₁ is Cl₃CO- and that the reaction is carried out in
29 toluene at reflux temperature.

31 When L is O the compound of formula (VI) may be in the
32 form of a reactive derivative thereof, which is often a
33 salt, such as the sodium or potassium salt.

35 The invention provides a further process for the
36 preparation of a compound of formula (I) wherein X is

- 9 -

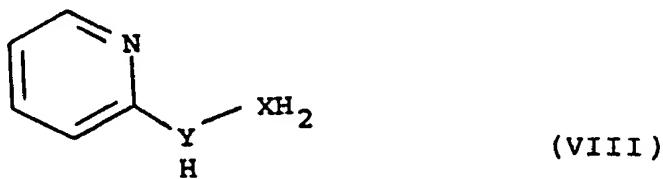
N, or a pharmaceutically acceptable salt thereof, which process comprising cyclising a compound of formula (VIII):



wherein the variables are as hereinbefore defined; and thereafter optionally converting any R₁ and/or R₂ group to another R₁/R₂ group respectively, converting Z¹ when other than Z, to Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

The cyclisation reaction may be effected by heating in an inert solvent, such as xylene or decalin or heating with a dehydrating agent, such as phosphorus oxychloride.

A compound of formula (VII) may be prepared by the reaction of a compound of formula (VIII):



01 - 10 -

02 with a compound of formula (IX):

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10 wherein Q_2 is a leaving group and the remaining
11 variables are as hereinbefore defined.

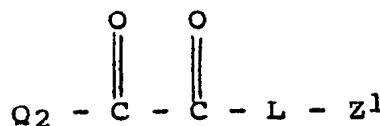
12

13 Q_2 is a leaving group as hereinbefore defined for Q_1
14 and the reaction is carried out in accordance with the
15 conditions described herein for the reaction between
16 the compounds of formulae (V) and (VI), wherein L is
17 NH.

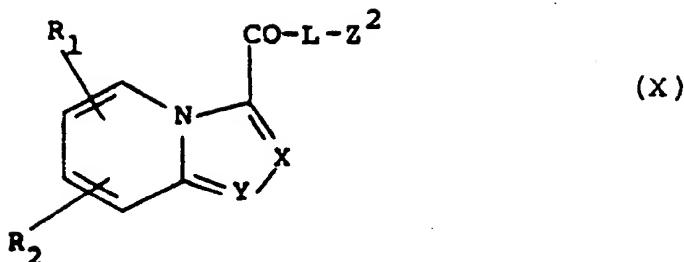
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19 It will be apparent that compounds of the formula (I)
20 containing an R_1 or R_2 group which is convertible to
21 another R_1 or R_2 group are useful novel intermediates.
22 i.e. a hydrogen substituent is convertible to a
23 halogen substituent by halogenation using conventional
24 halogenating agents.

25

26 Z^1 when other than Z may have a hydrogenolysable
27 protecting group which is benzyl optionally substituted
28 by one or two groups as defined for R_1 and R_2 . Such
29 benzyl groups may, for example, be removed, when R_1 or
30 R_2 is not halogen, by conventional transition metal
31 catalysed hydrogenolysis to give compounds of the
32 formula (X):

(IX):



wherein Z^2 is of formula (d) or (e):



wherein the variables are as defined in formula (I).

This invention also provides a further process for the preparation of a compound of the formula (I) which comprises N-alkylating a compound of formula (X), and optionally forming a pharmaceutically acceptable salt, of the resulting compound of the formula (I).

In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (X) by any group R_5/R_6 as hereinbefore defined. This may be achieved by reaction of the compound of formula (X) with a compound R_5Q_3 or R_6Q_3

01 - 12 -

02 wherein R₅ and R₆ are as hereinbefore defined and Q₃ is
03 a leaving group.

04 Suitable values for Q₃ include groups displaced by
05 nucleophiles such as Cl, Br, I, OSO₂CH₃ or
06 OSO₂C₆H₄pCH₃.

07 Favoured values for Q₃ include Cl, Br and I.

08 The reaction may be carried out under conventional
09 alkylation conditions for example in an inert solvent
10 such as dimethylformamide in the presence of an acid
11 acceptor such as potassium carbonate. Generally the
12 reaction is carried out at non-extreme temperature such
13 as at ambient or slight above.

14 Alternatively, 'N-alkylation' may be effected under
15 conventional reductive alkylation conditions when the
16 group R₅ or R₆ in the compound of formula (I) contains
17 a methylene group adjacent to the N-atom in the
18 bicyclic.

19 Interconverting R₅ or R₆ in the compound of the formula
20 (X) before coupling with the compound of the formula
21 (V) is also possible. Such interconversions are
22 effected conveniently under the above conditions. It
23 is desirable to protect any amine function with a group
24 readily removable by acidolysis such as a C₂-7 alkanoyl
25 group, before R₅/R₆ interconversion.

26 When R₅ or R₆ in the compound of formula (VI) contains
27 a methylene group adjacent to the N-atom in the bicyclic
28 it is often convenient in the preparation of such a
29 compound of formula (VI) to prepare the corresponding
30 compound wherein the methylene group is replaced by
31 -CO-, or for R₅ or R₆ is methyl, where the methyl group



- 13 -

is replaced by alkoxy carbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (V).

The compounds of formula (V), (VI), (VIII) and (IX) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of the formula (VI) wherein Z is of formula (c) may be prepared as described in European Patent Publication No. 115933 or by analogous methods thereto. Compounds of the formulae (VII) and (X) are novel and form an aspect of the invention.

It will be realised that in the compound of the formula (I) the -CO-L- linkage may have an endo or exo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo and exo isomer may if desired be synthesised from the corresponding endo or exo form of the compound of the formula (VI).

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT antagonists and it is thus believed may generally be

14
15 The invention also provides a pharmaceutical
16 composition comprising a compound of formula (I), or a
17 pharmaceutically acceptable salt thereof, and a
18 pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are
suitably adapted for oral or parenteral administration,
and as such may be in the form of tablets, capsules,
oral liquid preparations, powders, granules, lozenges,
reconstitutable powders, injectable and infusible
solutions or suspensions or suppositories. Orally
administrable compositions are preferred, since they
are more convenient for general use.

29 Tablets and capsules for oral administration are
30 usually presented in a unit dose, and contain
31 conventional excipients such as binding agents,
32 fillers, diluents, tabletting agents, lubricants,
33 disintegrants, colourants, flavourings, and wetting
34 agents. The tablets may be coated according to well
35 known methods in the art, for example with an enteric
36 coating.

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Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

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The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

8
9 For parenteral administration, fluid unit dose forms
0 are prepared containing a compound of the present
1 invention and a sterile vehicle. The compound,
2 depending on the vehicle and the concentration, can be
3 either suspended or dissolved. Parenteral solutions
4 are normally prepared by dissolving the compound in a
5 vehicle and filter sterilising before filling into a
6 suitable vial or ampoule and sealing. Advantageously,
7 adjuvants such as a local anaesthetic, preservatives
8 and buffering agents are also dissolved in the
9 vehicle. To enhance the stability, the composition can
20 be frozen after filling into the vial and the water
21 removed under vacuum.

22
23 Parenteral suspensions are prepared in substantially
24 the same manner except that the compound is suspended
25 in the vehicle instead of being dissolved and
26 sterilised by exposure of ethylene oxide before
27 suspending in the sterile vehicle. Advantageously, a
28 surfactant or wetting agent is included in the
29 composition to facilitate uniform distribution of the
30 compound of the invention.

31
32 The invention further provides a method of treatment or
33 prophylaxis of migraine, cluster headache, trigeminal
34 neuralgia and/or emesis in mammals, such as humans,
35 which comprises the administration of an effective
36 amount of a compound of the formula (I) or a
37 pharmaceutically acceptable salt thereof.
38



- 17 -

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.5 to 1000mg for example 1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.001 to 50mg/kg/day, more usually 0.002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions illustrate the preparation of intermediates.

- 18 -

01

02

Description 1

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04

(endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)

05

ethyl oxamate (D1)

06

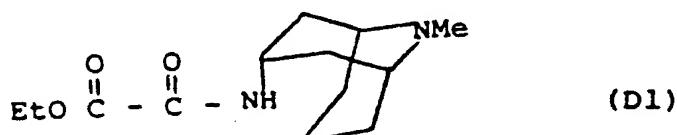
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To a stirred solution of (endo)-9-methyl-9-azabicyclo-[3.3.1]-nonan-3-amine (5.0g) and triethylamine (5ml) in CH_2Cl_2 (200ml) at 0°C was added, dropwise, a solution of ethyl oxalyl chloride (4.0ml) in CH_2Cl_2 (10ml). After 1h, the reaction mixture was washed with saturated NaHCO_3 solution (100ml), dried (K_2CO_3) and concentrated in vacuo. Trituration of the residue with ether afforded the title compound (D.1) (5.3g).

21

22

m.p. 105-90°C

23

24

 $^1\text{H-nmr}(\text{CDCl}_3)\delta$ 7.0 -6.5 (m, 1H)

4.2 (q superimposed on m, 3H)

3.2 -2.8 (m, 2H)

2.6 -0.8 (m, 16H including 2.40, s, 3H
and 1.35, t, 3H).

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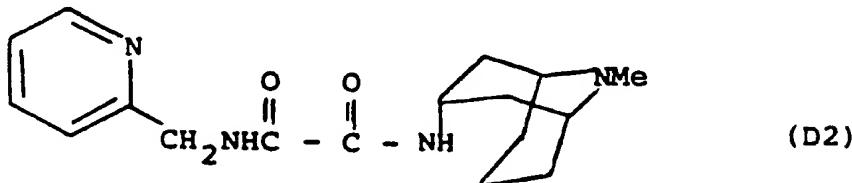
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- 19 -

Description 2

01
 02
 03
 04 (endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)
 05 -N'-(2-pyridyl-methyl)oxamide (D.2)
 06
 07
 08
 09



17 A solution of 2-aminomethyl pyridine (0.42g) and
 18 (endo)-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl) ethyl
 19 oxamate (D.1) (1.0g) in xylene (10ml) were heated under
 20 reflux until the reaction was complete by T.L.C. The
 21 solvent was removed in vacuo and the residue triturated
 22 with ether/petrol to give the title compound (D.2)
 23 (0.63g).

24
 25 $^1\text{H-nmr}(\text{CDCl}_3)\delta$ 8.7 -8.2 (m, 2H)
 26 7.7 -6.8 (m, 4H)
 27 4.5 (d, 2H)
 28 4.6 -3.8 (m, 1H)
 29 3.2 -2.7 (m, 2H)
 30 2.65-0.8 (m, 13H including 2.40, s, 3H)
 31

- 20 -

01

02

Example 1

03

04

(endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)
imidazo[1,5-a]pyridine-3-carboxamide (E1)

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A solution of (endo)-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-N'-(2-pyridylmethyl)oxamide (D.2) (0.3g) in xylene (10ml) was treated with phosphoryl chloride (0.1ml) and then heated under reflux for 18h. The solvent was then removed by evaporation in vacuo and the residue partitioned between CH_2Cl_2 (100ml) and K_2CO_3 solution. The organic extract was dried (K_2CO_3), evaporated and purified by column chromatography on silica to give the title compound (0.1g).

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$^1\text{H-nmr}(\text{d}^6\text{DMSO})\delta$	9.45	(d, 1H)
	8.00-7.75	(m, 1H)
	7.63	(d, 1H)
	7.46	(s, 1H)
	7.00	(t, 1H)
	6.85	(t, 1H)
	4.60-4.40	(m, 1H)
	3.20-3.00	(m, 2H)
	2.54	(s, 3H)
	2.45-2.27	(m, 2H)
	2.15-1.90	(m, 3H)
	1.65-1.40	(m, 3H)
	1.05-1.00	(m, 2H)

m.s. M^+ 298.1798; $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}$ requires M^+ 298.1793.

01

- 21 -

02

Example 2

03

04

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)
indolin-3-carboxamide (E2)

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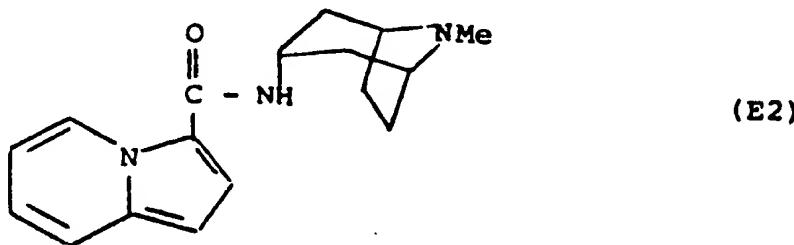
33

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37



A solution of (endo)-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (1.0g) and triethylamine (1.0ml) in CH_2Cl_2 (10ml) was added to a stirred solution of indolin-1-carbonyl chloride (J. Chem. Soc. C. 901 [1969]) (1.4g) in CH_2Cl_2 (100ml). After 1h, the reaction mixture was washed with K_2CO_3 solution, dried (K_2CO_3) and evaporated to dryness. Purification by column chromatography on alumina gave the title compound (0.5g) mp 102-3°

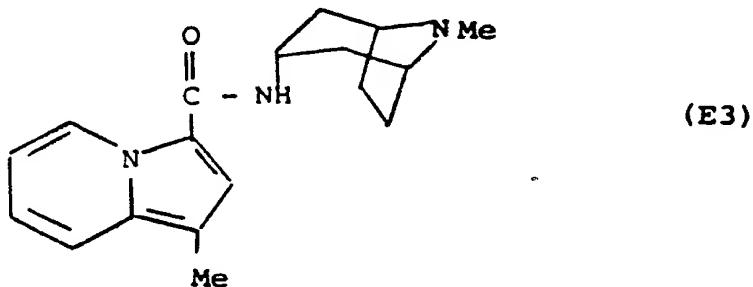
$^1\text{H-nmr}(\text{CDCl}_3)\delta$	9.56	(d, 1H)
	7.45	(d, 1H)
	7.06	(d, 1H)
	6.92	(t, 1H)
	6.72	(t, 1H)
	6.45	(d, 1H)
	6.25	(brd, 1H)
	4.30	(q, 1H)
	3.23	(brs, 2H)
	2.50-2.10	(m, 7H including 2.34, s, 3H)
	2.00-1.70	(m, 4H)

m.s. M^+ 283.1685; $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}$ requires M^+ 283.1685.

- 22 -

Example 3

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-
1-methylindolizin-3-carboxamide (E3)



Following the procedures outlined in Example 2;
 3-methyl-indolizin-1-carbonyl chloride (0.3g) was
 converted to the title compound (E.3) (0.16g) mp
 169-70°.

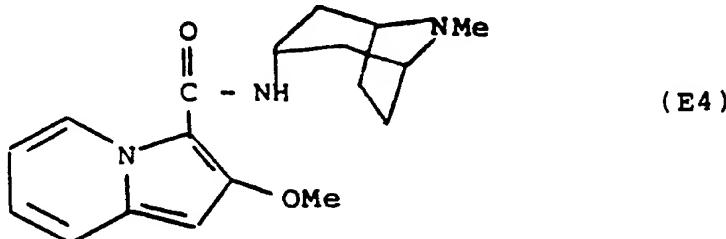
¹H-nmr (CDCl₃)δ 9.52 (d, 1H)
 7.38 (d, 1H)
 6.88 (s, t, 2H)
 6.67 (t, 1H)
 6.17 (d, 1H)
 4.28 (q, 1H)
 3.25 (brs, 2H)
 2.40-2.10 (m, 10H including 2.34, s, 6H)
 2.00-1.75 (m, 4H)

m.s. M⁺ 297.1844; C₁₈H₂₃N₃O requires M⁺ 294.1841.

- 23 -

Example 4

01
 02
 03
 04 (endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-
 05 2-methoxyindolin-3-carboxamide (E4)



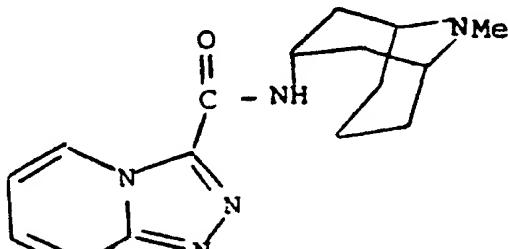
15 Following the procedures outlined in Example 2;
 16 2-methoxy-indolin-1-carbonyl chloride (0.3g) was
 17 converted to the title compound (0.22g)

18
 19 $^1\text{H-nmr}(\text{CDCl}_3)\delta$ 9.75 (d, 1H)
 20 7.68 (d, 1H)
 21 7.30 (d, 1H)
 22 6.94 (t, 1H)
 23 6.68 (t, 1H)
 24 6.08 (s, 1H)
 25 4.33 (q, 1H)
 26 4.04 (s, 3H)
 27 3.20 (brs, 2H)
 28 2.40-2.22 (m, 5H including 2.34, s, 3H)
 29 2.20-2.05 (m, 2H)
 30 2.00-1.85 (m, 2H)
 31 1.75 (d, 2H)

32
 33 m.s. M^+ 313.1794; $C_{18}H_{23}N_3O$ requires M^+ 313.1790.

34

- 24 -

Example 5(endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-pyrido[2,1-c]-S-triazole-3-carboxamide (E5)

(E5)

A solution of (endo)-N-(9-methyl-9-azabicyclo[3.3.1]-non-3-yl)-N'-(2-pyridylamino)oxamide (prepared from 2-hydrazino-pyridine as in description 2) (2.0g) was heated under reflux in a Dean and Stark apparatus in xylene (200ml) with tosic acid (0.1g) for 24h. The xylene was removed and the residue partitioned between aqueous NaHCO_3 and CHCl_3 (200ml). The chloroform extract was dried (K_2CO_3) and evaporated to dryness. Crystallisation of the residue from EtOAc/petrol afforded the title compound (E5) (1.2g) m.p. $193-4^\circ\text{C}$.

$^1\text{H-nmr}$ (CDCl_3) δ : 9.36 (d, 1H)
 7.86 (d, 1H)
 7.41 (t, 1H)
 7.33 (d, 1H)
 7.02 (t, 1H)
 4.65-4.45 (m, 1H)
 3.14 (brd, 2H)
 2.62-2.44 (m, 5H including 2.52, s, 3H)
 2.10-1.90 (m, 3H)
 1.60-1.35 (m, 3H)
 1.05-1.00 (m, 2H)

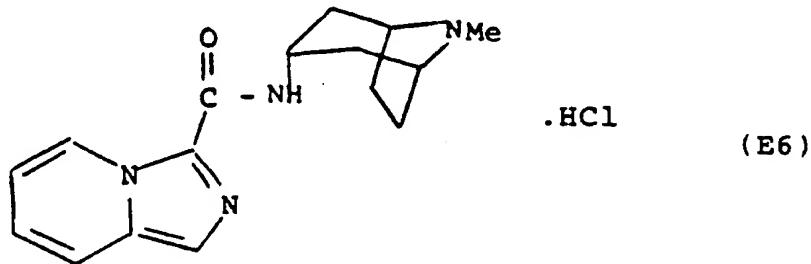
01

- 25 -

02 Following the procedures outlined in Description 1, 2
03 and Example 1, the appropriately substituted pyridine
04 and (endo)-8-methyl-8-azabicyclo[3.2.1]octan-3-amine
05 were converted into the following compounds.
06

07 Example 6

09 (endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)imidazo
10 [1,5-a]pyridine-3-carboxamide monohydrochloride (E6)



1H-nmr (d^6 -DMSO) δ

10.30 (br s, 1H)

9.35 (d, 1H)

8.43 (d, 1H)

7.82 (d, 1H)

7.63 (s, 1H)

7.20-7.00 (m, 2H)

4.10-4.00 (m, 1H)

3.90-3.70 (m, 2H)

2.64 (d, 3H)

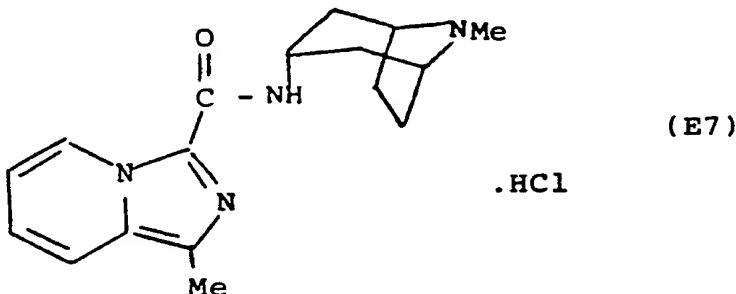
2.40-2.10 (m, 7H)

m.s. M^+ 284.1640; $C_{18}H_{20}N_4O$ requires M^+ 284.1649

- 26 -

Example 7

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methylimidazo[1,5-a]pyridine-3-carboxamide monohydrochloride (E7)



1H-nmr (CDCl₃) δ

12.35 (br s, 1H)

9.46 (br d, 1H)

7.57 (d, 1H)

7.10-6.80 (m, 2H)

4.37 (q, 1H)

3.80 (br s, 2H)

3.25-3.10 (m, 2H)

2.77 (d, 3H)

2.70-2.10 (m, 10H)

m.s. M⁺ 298.1799: C₁₇H₂₂N₄O₂ requires M⁺ 298.1804

01

- 27 -

02 Following the procedure outlined in Example 2: the
03 following compounds were prepared.

04

05 Example 8

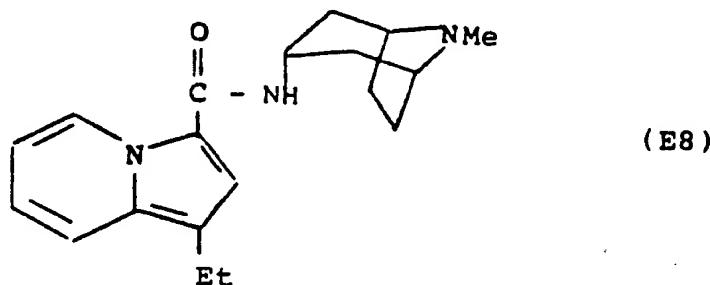
06

07 (endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-ethyl
08 indolizin-3-carboxamide (E8)

09

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m.p. 171-2°C

18

 $^1\text{H-nmr}$ (CDCl_3) δ

19

9.53 (dm, 1H)

20

7.40 (dm, 1H)

21

6.92-6.82 (m, 2H including 6.89, s, 1H)

22

6.67 (tm, 1H)

23

6.19 (brd, 1H)

24

4.29 (q, 1H)

25

3.25 (brs, 2H)

26

2.76 (q, 2H)

27

2.40-2.15 (m, 7H including 2.33, s, 3H)

28

1.95-1.72 (m, 4H)

29

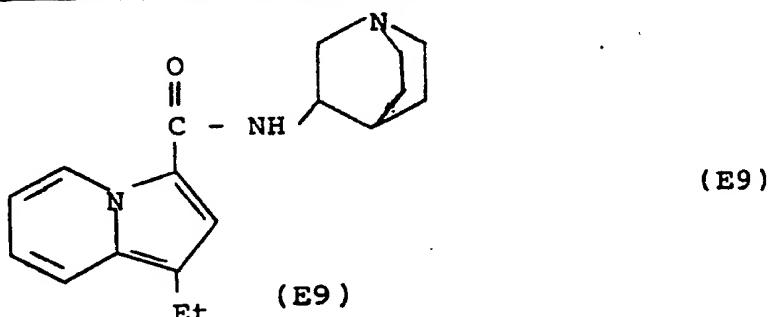
1.30 (t, 3H)

30

m.s. M^+ 311.2007; $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}$ requires 311.2017

31

- 28 -

Example 9N-(3-Quinuclidinyl)-1-ethylindolin-3-carboxamide (E9)

m.p. 185-6°C

¹H-nmr (CDCl₃) δ

9.54 (dm, 1H)
 7.40 (dm, 1H)
 7.05 (s, 1H)
 6.89 (tm, 1H)
 6.67 (tm, 1H)
 6.03 (brd, 1H)
 4.26-4.12 (m, 1H)
 3.48 (d,d,d, 1H)
 3.10-2.65 (m, 7H including 2.78, q, 2H)
 2.12-2.05 (m, 1H)
 1.92-1.70 (m, 3H)
 1.64-1.50 (m, 1H)
 1.30 (t, 3H)

m.s. M⁺ 297.1852: C₁₈H₂₃N₃O requires 297.1863

01

- 29 -

02

Example 10

03

04

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
phenylindolin-3-carboxamide (E10)

05

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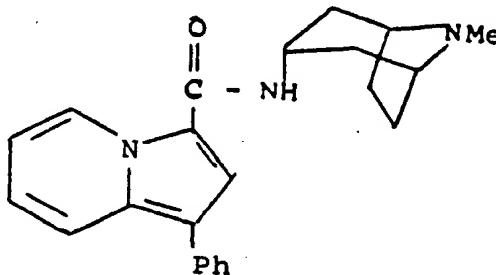
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(E10)

14

m.p. 148°C

15

¹H-nmr (CDCl₃) δ

16

9.65 (dm, 1H)

17

7.90-6.60 (m, 9H including 7.18, s, 1H)

18

6.30 (brd, 1H)

19

4.32 (q, 1H)

20

3.20 (brs, 2H)

21

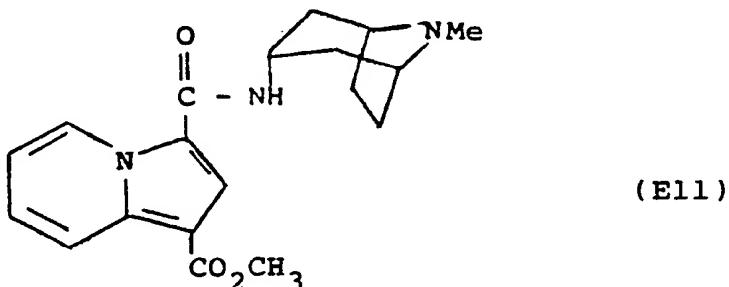
2.55-1.60 (m, 11H including 2.34, s, 3H)

22

- 30 -

Example 11

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-methoxycarbonylindolin-3-carboxamide (E11)



m.p. 183-4°C

$^1\text{H-nmr}$ (CDCl_3) δ

9.68 (dm, 1H)

8.27 (dm, 1H)

7.55 (s, 1H)

7.28 (m, 1H)

6.90 (dt, 1H)

6.31 (brd, 1H)

4.28 (q, 1H)

3.94 (s, 3H)

3.22 (brs, 2H)

2.55-1.55 (m, 11H including 2.34, s, 3H)

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- 31 -

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Example 12

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04

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
cyanoindolin-3-carboxamide (E12)

05

06

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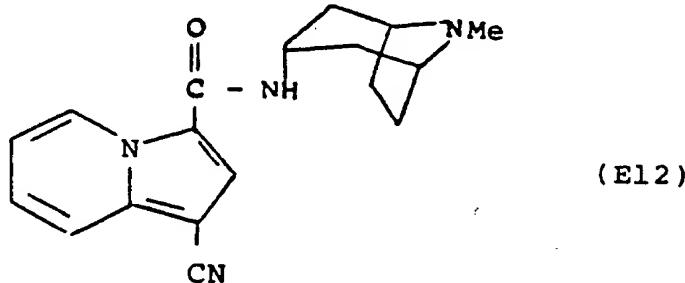
09

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m.p. 194-5°C

15

 $^1\text{H-nmr}$ (CDCl_3) δ

16

9.62 (dm, 1H)

17

7.70 (dm, 1H)

18

7.33 (s, 1H)

19

7.33-7.24 (m, 1H)

20

6.95 (dt, 1H)

21

6.33 (brd, 1H)

22

4.28 (q, 1H)

23

3.26 (brs, 2H)

24

2.41-2.20 (m, 7H including 2.33, s, 3H)

25

1.92-1.74 (m, 4H)

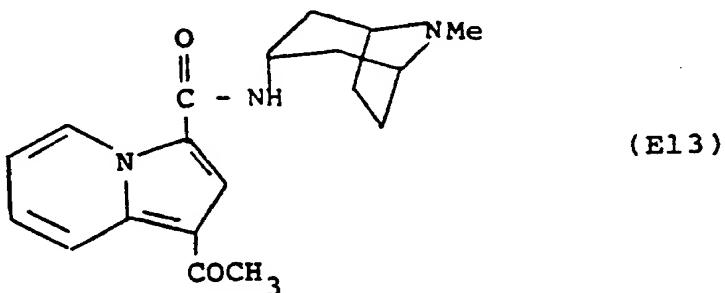
26

m.s. M^+ 308.1637; $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}$ requires 308.1637

27

Example 13

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-acetylindolin-3-carboxamide (E13)



m.p. 162-3°C

¹H-nmr (CDCl₃) δ

9.65 (d, 1H)

8.51 (d, 1H)

7.40 (s, 1H)

7.38-7.26 (m, 1H)

6.96 (t, 1H)

6.31 (brd, 1H)

4.31 (q, 1H)

3.25 (brs, 2H)

2.57 (s, 3H)

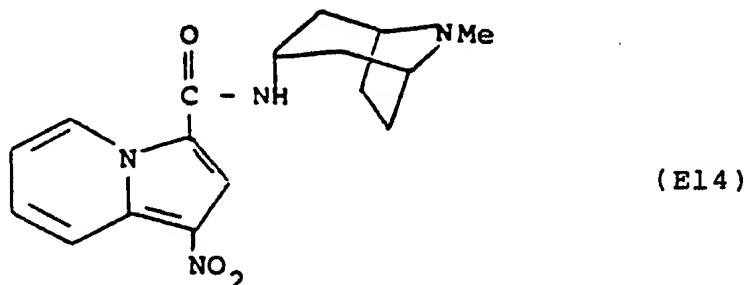
2.42-2.20 (m, 7H including 2.34, s, 3H)

1.95-1.75 (m, 4H)

m.s. M⁺325.1789; C₁₉H₂₃N₃O₂ requires 325.1788

01 - 33 -
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13Example 14

(endo)-N-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-nitro
indolin-3-carboxamide (E14)

14 m.p. 183-50C
15
16
17
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26

¹H-nmr (CDCl₃) δ

9.74 (d, 1H)
8.49 (d, 1H)
7.80 (s, 1H)
7.54 (t, 1H)
7.09 (t, 1H)
6.52 (brd, 1H)
4.30 (q, 1H)
3.28 (brs, 2H)
2.50-2.15 (m, 7H including 2.35, s, 3H)
2.00-1.80 (m, 4H)

m.s. M⁺ 328.1534; C₁₇H₂₀N₄O₃ requires 328.1537

- 34 -

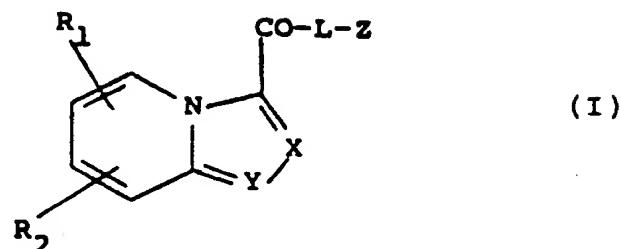
01
02 Pharmacology
0304 Antagonism of the von Bezold-Jarisch reflex
0506 The compounds were evaluated for antagonism of the von
07 Bezold-Jarisch reflex evoked by 5-HT in the
08 anaesthetised rat according to the following method:
0910 Male rats 250-350g, were anaesthetised with urethane
11 (1.25g/kg intraperitoneally) and blood pressure and
12 heart rate recorded as described by Fozard J.R. et al.,
13 J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A
14 submaximal dose of 5-HT (usually 6 μ g/kg) was given
15 repeatedly by the intravenous route and changes in
16 heart rate quantified. Compounds were given
17 intravenously and the concentration required to reduce
18 the 5-HT-evoked response to 50% of the control response
19 (ED₅₀) was then determined.
2021 The compounds of Examples 1 and 2 had an ED₅₀ value of
22 10mg/ μ g i.v. and the compound of Example 3 had an ED₅₀
23 value of 1.6 μ g/kg/ i.v.
24

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C

Claims

04 1. A compound of formula (I), or a pharmaceutically
05 acceptable salt thereof:



wherein

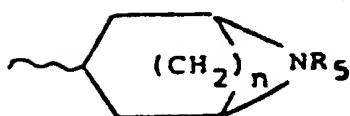
L is NH or O;

X is N or CR₃ wherein R₃ is hydrogen or C₁₋₆ alkoxy;
Y is N or CR₄ wherein R₄ is hydrogen, halogen, CF₃,
C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆
alkylsulphonyl, C₁₋₆ alkylsulphinyl, C₁₋₇ acyl, cyano,
C₁₋₆ alkoxy carbonyl, C₁₋₇ acylamino, hydroxy, nitro or
amino, aminocarbonyl, or aminosulphonyl, optionally
N-substituted by one or two groups selected from C₁₋₆
alkyl, C₃₋₈ cycloalkyl, and C₃₋₈ cycloalkyl C₁₋₄ alkyl
or disubstituted by C₄ or C₅ polymethylene; phenyl or
phenyl C₁₋₄ alkyl group optionally substituted in the
phenyl ring by one or two of halogen, C₁₋₆ alkoxy or
C₁₋₆ alkyl groups.

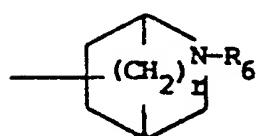
R₁ and R₂ are independently selected from hydrogen, or
halogen;

Z is a group of formula (a), (b) or (c):

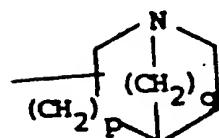
- 2 -



(a)



(b)

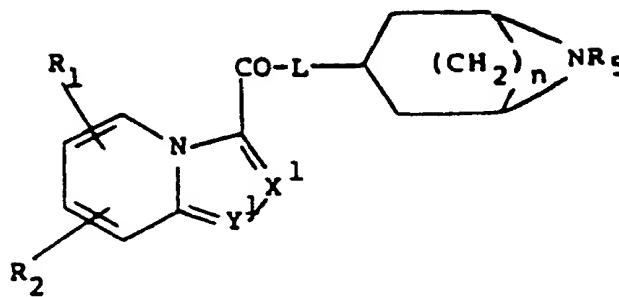


(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and

R₅ or R₆ is C₁₋₄ alkyl.

2. A compound according to claim 1 of formula (II):

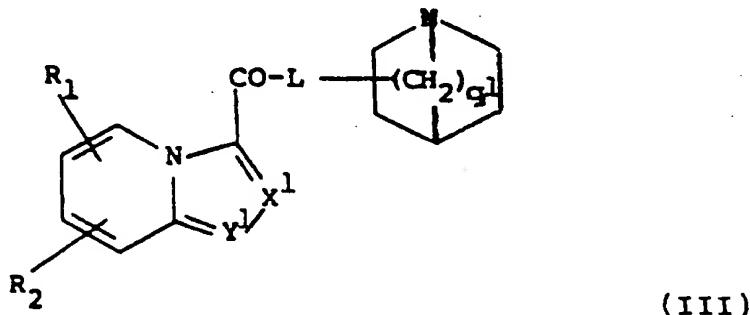


(II)

- 3 -

16 3. A compound according to claim 2 wherein R₅ is
17 methyl.

19 4. A compound according to claim 1 of formula
20 (III):



30 wherein the variable groups are as defined in claims 1
31 and 2.

33 5. A compound according to any one of claims 1 to 4
34 wherein Y is N, CH or CCH₃.

36 6. A compound according to any one of claims 1 to 5
37 wherein R_1 and R_2 are both hydrogen.

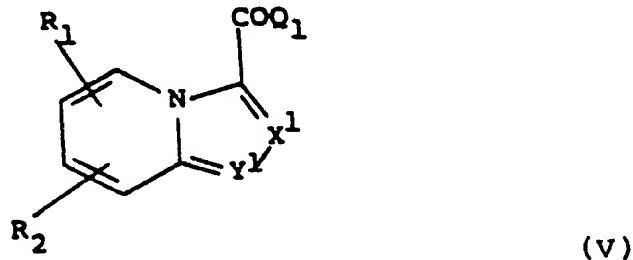
- 4 -

01
02 7. (endo)-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-
03 yl)imidazo[1,5-a]-pyridine-3-carboxamide,
04
05 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-
06 yl)indolizin-3-carboxamide,
07
08 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
09 methylindolizin-3-carboxamide,
10
11 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-
12 methoxyindolizin-3-carboxamide,
13
14 (endo)-N-(9-methyl-9-azabicyclo[3.2.1]non-3-
15 yl)pyrido[2,1-c]-S-triazole-3-carboxamide,
16
17 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-
18 yl)imidazo[1,5-a]-pyridine-3-carboxamide,
19
20 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
21 methylimidazo[1,5-a]pyridine-3-carboxamide,
22
23 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
24 ethylindolizin-3-carboxamide,
25
26 N-(3-quinuclidinyl)-1-ethylindolizin-3-carboxamide,
27
28 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
29 phenylindolizin-3-carboxamide,
30
31 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
32 methoxycarbonylindolizin-3-carboxamide,
33
34 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
35 cyanoindolizin-3-carboxamide,
36



01 - 5 -
02 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
03 acetylindolin-3-carboxamide,
04
05 (endo)-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1-
06 nitroindolin-3-carboxamide,
07
08 or a pharmaceutically acceptable salt of any of the
09 foregoing.

10
11 8. A process for the preparation of a compound
12 according to claim 1, which process comprises reacting
13 a compound of formula (V):



with a compound of formula (VI):



or a reactive derivative thereof, when L is O;

wherein Q₁ is a leaving group; Z¹ is Z as defined in
claim 1 or wherein R₅/R₆ is replaced by a
hydrogenolysable protecting group; and the remaining
variables are as defined in claim 1; and thereafter
optionally converting any R₁ and/or R₂ group to another
R₁/R₂ group respectively, converting Z¹,

- 6 -

when other than Z, to Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7, and a pharmaceutically acceptable carrier.

10. A compound according to claim 1 for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis, in mammals.



⑯ EUROPEAN PATENT APPLICATION

⑯ Application number: 87306548.6

⑯ Int. Cl.³: C 07 D 451/04
C 07 D 451/14, C 07 D 453/02
A 61 K 31/46, A 61 K 31/435

⑯ Date of filing: 24.07.87

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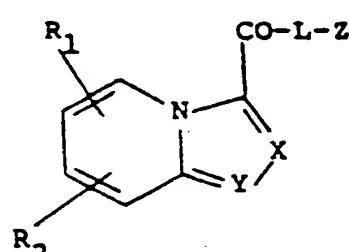
⑯ Date of publication of application:
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⑯ Azabicyclic compounds, process for their preparation, and their pharmaceutical use.
⑯ Compounds of formula (I), or a pharmaceutically acceptable salt thereof:



wherein

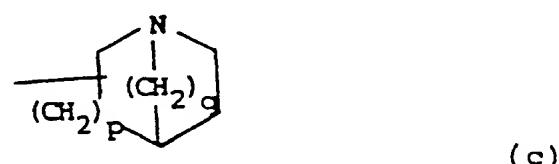
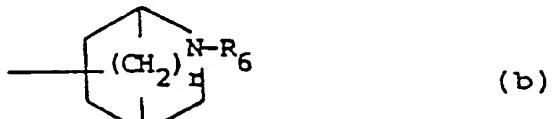
L is NH or O;

X is N or CR₃ wherein R₃ is hydrogen or C₁₋₆ alkoxy;

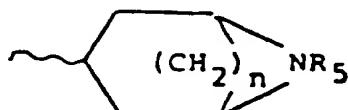
Y is N or CR₄ wherein R₄ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphinyl, C₁₋₇ acyl, cyano, C₁₋₆ alkoxy carbonyl, C₁₋₇ acylamino, hydroxy, nitro or amino, aminocarbonyl, or aminosulphonyl, optionally N-substituted by one or two groups selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, and C₃₋₈ cycloalkyl C₁₋₄ alkyl or substituted by C₄ or C₅ polymethylene; phenyl or phenyl C₁₋₄ alkyl group optionally substituted in the phenyl ring by one or two of halogen, C₁₋₆ alkoxy or C₁₋₆ alkyl groups.

R₁ and R₂ are independently selected from hydrogen, or halogen;

Z is a group of formula (a), (b) or (c):



wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; and R₅ or R₆ is C₁₋₄ alkyl; having 5-HT₃ antagonist activity, a process for their preparation and their use as pharmaceuticals.





DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	WO-A-8 501 048 (SANDOZ) * claims 2,3,12 *	1,10	C 07 D 451/04 C 07 D 451/14 C 07 D 453/02 A 61 K 31/46 A 61 K 31/435
A, P	EP-A-0 200 444 (BEECHAM GROUP) * claims 1, 12, 15, 17 *	1,8,9, 10	

TECHNICAL FIELDS
SEARCHED (Int. Cl.4)

A 61 K 31/435
A 61 K 31/46
C 07 D 451/04
C 07 D 451/14
C 07 D 453/02
C 07 D 519/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	03-02-1989	KNAACK
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document